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(71) Applicant *(for all designated States except US)*: **ULKAR KIMYA SANAYII VE TICARET ANONIM SIRKETI** [TR/TR]; Ulkar Kimya San. ve Tic. A.S., Organize Sanayi Bölgesi, Cerkezköy, 59500 Tekirdag (TR).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **ÜNSAL, Serafettin** [TR/TR]; Ulkar Kimya San. ve Tic. A.S., Organize Sanayi Bölgesi, Cerkezköy, 59500 Tekirdag (TR).

(74) Agent: **KAYACAN, Vildan**; Portakal Çiçegi Sok. 5/1, A.Ayranci, 06690 Ankara (TR).

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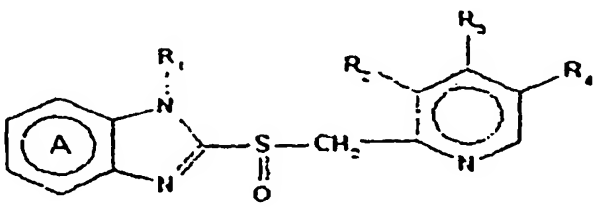
(54) Title: A METHOD OF ELIMINATING SULFONE ANALOG IN THE SYNTHESIS OF PYRIDINE-BENZIMIDAZOLE SULFOXIDES



(I)

(57) Abstract: Process for the preparation of pyridine-benzimidazole sulfinyl compounds such as Omeprazole, Lansoprozole and Pantoprozole of general formula (I), wherein the ring A may optionally be substituted, R_1 is hydrogen or an N-protecting group, each of R_2, R_3 and R_4 represent (1) a hydrogen atom, (2) alkyl group which may be substituted with halogen atom(s) or (3) an alkoxy group which may be optionally substituted with halogen atom(s) or alkoxy; or its salt. Sulphone analogs of the corresponding compounds as impurity are formed during oxidation of the precursor thioether of the compèound of formula (I). A process is provided for the elimination of sulphone analogs in contaminated products. The purification process comprises treatment of semi-pure benzimidazole derivatives with solid K_2CO_3 in alcohol medium at elevated temperatures.

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A METHOD OF ELIMINATING SULFONE ANALOG IN THE SYNTHESIS OFPYRIDINE-BENZIMIDAZOLE SULFOXIDES

FIELD OF INVENTION:

This invention relates to reducing the amount of sulfone impurity content of the product of formula(I) to below 0.5% which is formed during oxidation reaction of its corresponding sulfide.

BACKGROUND OF INVENTION:

Benzimidazole derivatives,2-(2-pridylmethylsulfinyl) benzimidazole derivatives of general formula (I) are produced from their corresponding sulphides by oxidation with an oxidising agent examplified by m-chloroperbenzoic acid, peracetic acid, trifluoroperacetic acid, permaleic acid, sodium bromite, sodiumhypochloride, hydrogen peroxide or any other reagent already described in the bibliography such as those listed by Madesclaire et al., in Tetrahedran,42,5454 (1986).In a number of patents regarding the production of compound (I) various methods are described. For example, in patent WO 00/78729 A1, international publication date 28.12.2000, crystalline forms of Lansoprazole are described. In this patent pharmaceutically advantageous crystalline forms of Lansoprazole are laid open.

In European patent 0302720 A1, date of publication 08.02.1989, production of 2-(2-pyridylmethylsulfinyl)-benzimidazole compounds is described. In this patent, production of compound (I) with the oxidation of its corresponding sulphide with hydrogen peroxide in the presence vanadium compounds in good yield and with low production of by product is laid open.

In another patent WO 98/21202 of publication date 22.05.1998, crystals of benzimidazole derivatives and their production is described.

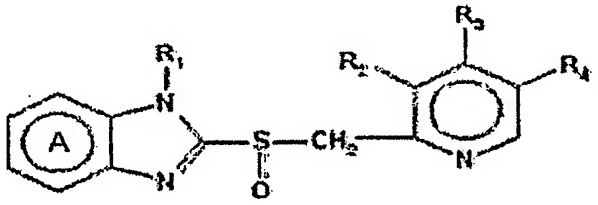
In this patent, a method is described for the production of substantially solvent-free and stable crystals of benzimidazole derivatives. In none of these inventions there is mention to formation or elimination of impurities in the form sulphone as reaction by product when the last phase of oxidation of the corresponding sulphide to sulphoxide is being carried out. Oxidation reactions should be carefully controlled. Over oxidisation and many other factors may cause the formation of sulphonic impurities which are difficult to eliminate by known purification methods such as recrystallisation, due to formation of mixed crystals with sulphoxide. Sulphone derivatives may also form at the earlier stages or even at the

beginning of oxidation reaction and may end up with 3-10%by weight as sulphone contaminated finished product.

Chromatographic separation methods are difficult and costly in addition to being not practical for industrial scale productions. Therefore inventors of the present invention had to find a method for eliminating sulphonic derivatives as an impurity mixed with sulphoxide crystals. This is achieved by treating contaminated product with K_2CO_3 in solid form in aqueous alcohol medium at elevated temperatures, filtering the mixture as hot to remove undissolved K_2CO_3 crystals and cooling the solution to precipitate the product. This sulphone-free product is isolated, washed or suspended in water to remove the crystal alcohol and crystal water. Thus obtained crude product is further recrystallised in a suitable solvent.

DESCRIPTION OF THE INVENTION:

This invention relates to production of sulphone free 2-(2-pyridinylmethylsulfinyl)-1H-benzimidazole derivatives of general formula (I) which are of value as a medicine for example as an anti-ulcer agent and so on,

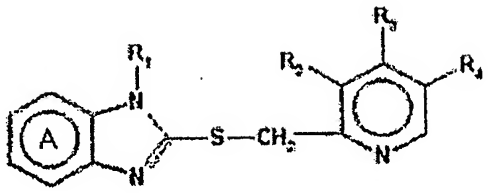


(I)

wherein ring A may optionally be substituted, R^1 is an N-protecting group or hydrogen, R^2,R^3,R^4 each represents (1) a hydrogen atom, (2) an alkyl group which may be substituted optionally with halogen atom(s) or (3) an alkoxy group which may optionally be substituted with halogen atom(s) or alkoxy; or its salt.

The term "sulphone-free" product used in this text will represent a compound of formula(I) with a sulphone content as an impurity lower than 0.5% as required by many analytical specifications.

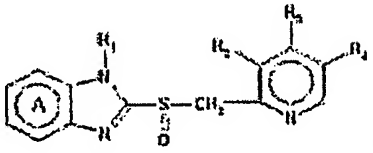
Compound (I) is prepared by oxidation of its corresponding sulphide of formula (II) with an oxidizing agent in a suitable solvent.



oxidizing agent

(II) SULPHIDE

solvent



Compound (I) SULPHOXIDE

wherein for compound (II).R^1,R^2,R^3,R^4 has the same meaning as mentioned above for compound (I)

N-protecting group in compound (I) and (II) is an alkyl group, a carbamoyl group, an alkyl carbamoyl group, an acyl group, a carboalkoxy group, a dialkyl carbomoyl group, an alkylsulfonyl group, an alkoxy carbonyl methyl group or an alkylcarbonylmethyl group,

R^1 in compound (I) and (II) is a hydrogen group,

Ring A of compound (I) and (II) is an alkoxy group, which may optionally be substituted with halogen,

Ring A of compound (I) and (II) is unsubstituted, R^3 in compound (I) and (II) is C_{1-4} alkoxy which may optionally be substituted with fluorine(s) or C_{1-4} alkoxy -C_{1-8} alkoxy R^4 is methyl or hydrogen atom

The salt of formula (I) is pharmaceutically acceptable salt. Example of salts are salts of inorganic bases, salts of organic bases or salts of basic amino acids. Preferred ones are the salts of inorganic bases of alkali metals sodium or potassium,salts of alkaline earth metals such as calcium and magnesium and ammonia salts. Salts of organic bases are preferred as of trimethyl amine, triethyl amine, picoline, ethanol amine, pyridine, diethanol amine, triethanol amine.

Preferred salts of basic amino acids are of lysine, arginine, etc.

Compounds of general formula (I) are known as common international denominations

Such as :

Omeprazole[A ring substituted with OCH_3 , R_2 and $R_4 = CH_3$ and $R_3 = OCH_3$]

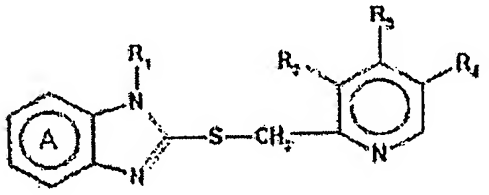
Lansoprazole[A ring is not substituted, $R^2 = CH_3$, $R^3 = OCH_2\text{-}CF_3$, $R^4 = H$]

Pantoprazole[A ring substituted with $-OCF_2$, $R^2 = CH_3$, $R^3 = OCH_3$ and $R^4 = H$]

Oxidation reactions can be performed with numerous oxidizing agents such as those listed by Madesclaire et al., in Tetrahedron, 42, 5459 (1986) also by use of m-chloroperbenzoic acid, sodiummetaperiodate, iodobenzene, hydrogen peroxide usingVanadium catalysts .Inventors have experienced that use of m-chloroperbenzoic acid present many advantages as far as formation of low content of sulphonic by-products are concerned. The oxidizing agent is used preferably in approximately equivalent or a little excess amount relative to sulphide compound, more preferably about 1-1.5 equivalent. Also the use of dichloromethane and chloroform as reaction solvent cooled to -20°C or lower reaction temperatures helps low accumulation of impurities.One other factor that helps low formation of sulphonic derivatives is the slow addition of oxidizing agent as within 8-10 hours.

These precautions taken for controlled oxidation will not prevent the over oxidation of sulphoxides to their sulphone analogs.

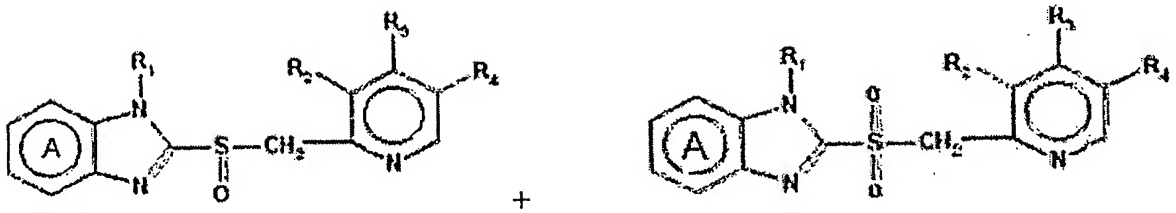
There are many factors which will accelerate this formation, such as reaction temperature, type of oxidizing agent employed, quality of the compound (II), reaction time, type of the solvent in which the reaction is carried out etc. Sulphonic impurity can be isolated and well characterized by means of its spectral data and verified under the HPLC analysis. HPLC is capable of identifying the sulphone analogs along with other impurities and determining their amounts both during the reaction and in the isolated finished product.



(II) SULPHIDE

Oxidizing agent

solvent



(I) SULPHOXIDE (III) SULPHONE

Inventors of the present invention had to develop a process to eliminate this impurity for the purpose of providing sulphone-free crystals of Omeprazole, Lansoprazole and Pantoprazole which are of value as medicine .

DETAILS OF THE INVENTION :

At the end of oxidation reaction, that is when all of product (II)is converted to its sulphoxide derivative (I), amount of sulphonic impurity formed as by-product is determined by HPLC. Reaction solvent is evaporated and to the precipitate formed aqueous 90-96 % lower alcohol preferably 90% $^{v}/_{v}$ ethyl alcohol is added. Slurry is heated to 55-60 °C to obtain a solution. To this solution K_2CO_3 crystals are added and the mixture was kept under stirring at the same temperature for a period of time. Hot mixture is filtered to remove the insolubles mainly consisting of undissolved K_2CO_3 crystals. Clear filtrate is ice- cooled so as to precipitate the solvated and sulphone-free crystals of the product of formula (I). Precipitate is recovered by filtration. Crystals of this compound contain water and alcohol in its crystal structure. Crude product is washed with plenty of water to remove the alcohol and basic water (K_2CO_3 is dissolved in water) or suspended in water as described in patent of international publication number: WO 98/21201. Crude product may optionally be dried or a well-drained wet cake is further subjected to recrystallisation in a suitable solvent.

It is of high importance that residual solvent in the crystal structure of the crude product must be as low as possible in advance of recrystallisation process. Amount of solid K_2CO_3 that should be added to aqueous ethyl alcohol solution of product (I) is related to the amount of product (III),that is amount of sulphonic impurity present. HPLC analysis of the

oxidation reaction product can easily determine the quantity of sulphone analog on peak area basis. Inventors have experienced that this may be 1 % or higher upto 10 %.

Although there is no formula to calculate the exact amount of added K_2CO_3, over usage than necessary will cause lower yields due to partial decomposition of sulphoxide.

Insufficient usage however, will not reduce the sulphone under desired limits (single impurity limit, not more than 0.5 %) as required by many analytical specifications.

Many experiments were done concerning the optimum amount of solid K_2CO_3 that should be added. Best results were obtained as follows:

-If sulphone content of the contaminated sulphoxide is between 1-5 %; amount of K_2CO_3 that should be added is 10 % by weight of the sulphide charged for oxidation.

-If sulphone content is higher than 5 %; weight of K_2CO_3 added is 15-20 % of weight of the sulphide subjected to oxidation.

These are preferred figures and do not limit the scope of the invention.

The alcohol used as treatment medium includes C_{1-6} alcohols (e.g. ethanol,isopropyl alcohol,methanol,etc.). Best results were obtained by using ethanol. Aqueous alcohol may be 90% $^{v}/_{v}$ to 96% $^{v}/_{v}$ in concentration. Aqueous alcohol particularly preferred is 90% $^{v}/_{v}$ ethyl alcohol.

Amount of aqueous alcohol in which the sulphoxide dissolved is optional, however excess amounts will cause lower yields due to known solubility property of the product in ethyl alcohol. Preferred amount will be 5 to 10 fold of the weight of the sulphide subjected to oxidation. Solid K_2CO_3 addition and mixing temperature in alcohol medium is 40-65 °C. Preferred treatment temperature is 55-60 °C. Treatment period of alcoholic solution of sulphoxide with K_2CO_3 crystals is about 20-30 minutes. Thus treated mixture is filtered as still hot by the known methods of filtration to eliminate the remaining undissolved K_2CO_3 crystals along with other insolubles. Usage of filtration aids such as celites, hyflosupercell etc, is recommended to achieve a clear filtrate. Filtrate is cooled to about –5 °C and kept under agitation for several hours (2-3 hours) at this temperature so the product is precipitated. Precipitate is either vacuum filtered or centrifuged. Wet cake is washed several times with plenty of deionized water in order to remove alcoholic mother liquor and to remove crystal water or suspended in water at room temperature and stirred for 1-2 hours and re-filtered and washed with water for the same purpose.

Filtered cake is sucked to dryness under vacuum, or the centrifuge is spinned to dryness in order to minimize remaining water or the product may optionally be dried in vacuo at a temperature of 20-60 °C, preferably at 50 °C for about 10-20 hours.

Thus obtained sulphon-free crude product is subjected to recrystallisation in a suitable solvent. For Omeprazole, Lansoprazole and Pantoprozole better crystalline structures possessing the desired whiteness have been obtained by use of ethyl acetate as recrystallisation medium.

Details of this invention are illustrated in the following examples, but invention is not limited to these examples.

EXAMPLE 1

Production of 2-[[3-methyl-4-(2,2,2-trifluoroethoxy)-pyridin-2-yl] methyl sulfinyl] benzimidazole :

40 kg of 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-pyridin-2-yl]-methyl]thio] benzimidazole monohydrate was added into a vessel containing 1400 kg of chloroform. Mixture was cooled to -20°C with stirring. At this temperature 32 kg of m-chloroperbenzoic acid dissolved in 560 kg of chloroform was added to reaction vessel very slowly. Rate of addition was so adjusted that it took 8 hours to end the oxidation. Amount of the unreacted sulphide and the amount of sulphonic impurity being formed was determined by HPLC at the end of reaction.

Unreacted sulphide was 0.8 % and sulphone analog formed was 3.3 % calculated as based on peak area percentage. To the reaction medium 500kg water was added and temperature was allowed to rise to 20-25°C. At this temperature 120 kg of 25 % $^{w}/_{w}$ K_2CO_3 solution was added and pH of mixture was measured as 9.9. Phases were separated. Organic phase was distilled off under reduced pressure to dryness. To the remaining off white residue 400 liters of 90 % $^{v}/_{v}$ ethanol was added and the mixture was heated at 60°C. At this temperature to the clear solution 4 kg of solid K_2CO_3 was added, and keeping the temperature same, mixture was stirred for 30 minutes. Some of the K_2CO_3 crystals remained undissolved. The mixture as hot was filtered to crystallization vessel and gradually cooled to -5°C. Precipitated product was left under agitation for 3 hours at this temperature fallowed by centrifugation. Centrifuge was spinned to dryness and washed

with 1500 liters of deionized water three times. Centrifuge was spin dried. Wet cake was directly taken to recrystallisation. A sample of crude product was analyzed by HPLC. Results were found in the crude product as sulphide content 0.1 % and sulphone analog 0.3 %.

Recrystallisation of Crude Product:

40 kg of wet crude product as obtained above was added into 800 liters of ethyl acetate and vessel content was heated to 55°C. To the clear solution obtained active carbon was added, and mixture was filtered. Clear and colorless solution was heated and ethyl acetate was distilled off under reduced pressure till about 200 liters of solution remained in the vessel. Vessel content was cooled to -5°C with stirring and the slurry was aged for 3 hours. Pure product was centrifuged and dried for 8 hours at 40°C in vacuo to yield 24 kg of as white powder.

EXAMPLE 2

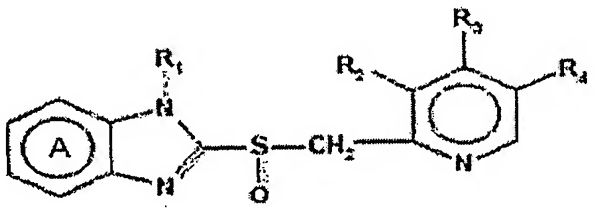
Production of 2-[[3-methyl-4-(2,2,2-trifluoroethoxy)-pyridin-2-yl] methyl sulfinnyl] benzimidazole :

To a mixture of 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-pyridin-2-yl]-methyl] thio] benzimidazole monohydrate (20g) in chloroform (500ml) was added dropwise peracetic acid (14g) mixed in chloroform (200ml) at -20°C over 8 hours. At the end of reaction, sulphone impurity mixed in crude product was determined as 3.7 % by HPLC analysis. 250 ml water was added to the reaction mixture and heated to 20-25°C. 60 g of 25 % K_2CO_3 solution was added and pH of the mixture was measured as 8.7. Phases were let to separate. Organic phase was distilled to dryness under vacuum. To the remaining residue 200 ml of 90 % $^{v}/_{v}$ aqueous ethyl alcohol was added and the mixture was heated at 55°C for about 30 minutes. To the clear solution obtained, 3.5 g of K_2CO_3 crystals were added followed by agitation for 30 minutes at the same temperature. Mixture was filtered as hot and was cooled down to -5°C to precipitate the crude product. Precipitate was stirred at -5°C for 4 hours and then filtered. Filter was sucked to dryness and then washed with 1 liter of deionized water three times. A sample was taken from wet cake for HPLC analysis. Sulphone analog was found to be 0.4 % 24.5 g of wet crude product was obtained. This

product was then taken to recrystallisation in ethyl acetate as described in example 1 (recrystallisation of crude product).

CLAIMS

1. A method for producing sulphone-free pyridine benzimidazole sulfinyl compounds of general formula (I)



(I)

wherein the ring A may optionally be substituted, R^1 is hydrogen or an N-protecting group , each of R^2,R^3,R^4 represent (1) a hydrogen atom,(2) alkyl group which may be substituted with halogen atom(s) or (3) an alkoxy group which may be optionally substituted with halogen atom(s) or alkoxy;

or its salt,which comprises the treatment of semi-pure and sulphone contaminated products of formula (I) with solid K_2CO_3 in 90 % v/v aqueous ethyl alcohol at elevated temperatures.

Sulphone analogs of compound (I) can be formed during oxidation of their corresponding sulphides to sulphoxides, therefore it is the object of this invention to reduce the amount of sulphone impurity to lower than 0.5% in pure product.

2. The method as claimed in Claim 1 comprises the oxidation of sulfinyl derivatives (compound II) to their corresponding sulphoxides (compound I) by using an oxidizing agent.

The oxidizing agent is used preferably in approximately equivalent or a little excess amount relative to compound (II), more preferably 1-1.5 equivalent.

3. The oxidizing agent to be employed according to Claim 2 is characterized in that can be examplified by those listed by Madesclaire et al. , in Tetrahedron ,42,5459(1986),also can be peracetic acid,m-chloroperbenzoic acid,sodiummetaperiodate,iodobenzene,hydrogen peroxide.

4. The process according to Claims 1,2 and 3 is characterized in that sulphone contaminated compound (I) is treated with solid K_2CO_3 in 90% v/v aqueous ethyl alcohol at 40-60 ^{0}C , preferably at 50-55^{0}C for about 30 minutes.

5. Amount of solid K_2CO_3 to be added to the alcoholic solution of compound (I) according to Claim 4 is characterized in that, is the 10% of the weight of the sulphide subjected to oxidation if sulphone content is between 1-5%.

6. Amount of solid K_2CO_3 to be added to the alcoholic solution of compound (I) according Claim 4 is characterized in that, is 15-20% of the weight of sulphide subjected to oxidation if sulphone content is higher than 5%.

7. The process according to Claim 4 wherein amount of 90% v/v aqueous ethyl alcohol in which sulphone contaminated sulphoxide will be dissolved is 5 to 10 fold of the weight of sulphoxide.

8. The process according to Claims 4,5,6,7,8 and 9 is characterized in that solid K_2CO_3 that remains undissolved in hot alcoholic mixture is removed either by filtration or centrifugation fallowed by ice-cooling and precipitation and collecting the precipitate by filtration or centrifugation.

9. The process according to Claim 9 wherein during filtration or centrifugation of hot alcohol and solid K_2CO_3 mixture ,filter aid is used so that a clear filtrate is obtained and wherein filter aid employed is celites and kieselguhr.

10. The process according to Claim 9 is characterized in that after ice cooling ,the obtained precipitate is filtered or centrifugated fallowed by washing with plenty of deionized water several times or the obtained precipitate is suspended in water at ambient temperature , stirred for a period of time and refiltered or centrifugated.

11. The process according to Claim 9 and 11 wherein sulphone free precipitate is recrystallized in ethyl acetate either as dry or as a wet cake.

12. The process according to Claim 1 is characterized in that pyridine benzimidazole derivatives are Omeprazole,Lansoprazole and Pantoprazole.

INTERNATIONAL SEARCH REPORT

Internati Application No
PCT/TR 02/00058

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6 245 913 B1 (KULKARNI DILIP GANESH ET AL) 12 June 2001 (2001-06-12) column 4, line 12 - line 40	1-12

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
10 January 2003	24/01/2003

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

Internati Application No
PCT/TR 02/00058

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6245913 B1	12-06-2001	NONE	